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ASSINATURAS PROTEICAS DAS GLÂNDULAS ANEXAS E TESTÍCULOS DE RATOS OBESOS E DIABÉTICOS

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BOTUCATU, SÃO PAULO
MARÇO – 2024

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Tese apresentada junto ao Programa de Pós-graduação em Biotecnologia Animal para obtenção do título de DOUTOR.

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RESUMO

CARVALHO, M.G. **ASSINATURAS PROTEICAS DAS GLÂNDULAS ANEXAS E TESTÍCULOS DE RATOS OBESOS E DIABÉTICOS**. Botucatu – SP 2024. 424p. Defesa (Doutorado). Faculdade de Medicina Veterinária e Zootecnia, Campus Botucatu, Universidade Estadual Paulista.

A incidência crescente da obesidade e do diabetes representa um desafio significativo para a saúde pública mundial. Na faixa etária dos jovens em idade reprodutiva, a prevalência dessas condições é alarmante, atingindo 19,8% para a obesidade e 8,5% para o diabetes. Além disso, essas doenças estão ligadas à disfunção hormonal e erétil, comprometendo a morfologia e a qualidade dos espermatozoides. Os processos inflamatórios e o estresse oxidativo resultantes de irregularidades na sinalização da glicose e insulina são fatores determinantes para a atrofia e deterioração funcional dos testículos e glândulas associadas, contribuindo significativamente para a infertilidade masculina. Nesse sentido, pretende-se compreender os efeitos da síndrome metabólica na função testicular, próstata e vesícula seminal, utilizando a proteômica para identificar biomarcadores para diagnóstico ou prognóstico da infertilidade masculina. Foram utilizados 30 ratos Wistar com aproximadamente 50 dias de idade, separados em 3 grupos: controle (n = 10), diabéticos (n = 10) e obesos (n = 10). O grupo obeso recebeu dieta de cafeteria e água *ad libitum* com 5% de sacarose, por 38 semanas, simultaneamente os grupos controle e diabéticos receberam ração comercial balanceada e água *ad libitum*. Os animais foram pesados uma vez por semana, para avaliação da evolução do peso para cálculo do índice de *Lee*. O diabetes foi induzido com aplicação de 35 mg/kg de estreptozotocina, dose única, e foram considerados diabéticos animais com perda de peso corporal e níveis de glicemia maiores ou iguais a 200 mg/dL. Os testículos, próstata e vesícula seminal, foram dissecados e preparados para proteômica a qual utilizou a abordagem *shotgun* (CEUA, n 0212/2022). Os dados foram submetidos a análise multivariada (*principal componente analysis*) e a univariada (ANOVA e teste de Fisher LSD). Curvas ROC foram construídas para grupos tratados (diabéticos ou obesos) *versus* controle, considerando AUC > 0,80 e P < 0,05. Na análise de componentes principais (PCA) realizada na próstata e no fluido da vesícula seminal, observou-se uma clara separação apenas no grupo de diabéticos, destacando a identificação de 23 e 8 proteínas, respectivamente, com abundância diferencial. Já no testículo, a PCA revelou uma distinção entre os grupos controle, diabético e obeso, conforme evidenciado pelo *heatmap*. Nesse contexto, foram identificadas 80 proteínas com abundância diferencial, distribuídas em diferentes localizações celulares, como citoplasma, acrossomo da célula espermática, mitocôndria e núcleo. A maioria dessas proteínas são produzidas nos testículos humanos. Além disso, na análise das interações proteína-proteína, foram identificadas vias relevantes, como Wnt e spliceossomo, juntamente com alterações nas atividades enzimáticas das vias de glicólise/gliconeogênese. Este estudo revela que as proteínas identificadas estão intimamente ligadas à atividade androgênica, motilidade espermática, integridade celular, proteção contra estresse oxidativo e fertilização. Essas descobertas oferecem *insights* valiosos sobre possíveis biomarcadores associados às glândulas sexuais acessórias e células testiculares em contextos de diabetes e obesidade. Notavelmente, os efeitos foram mais pronunciados entre os indivíduos diabéticos, enquanto nos obesos foram observados mecanismos compensatórios. Essas conclusões destacam a importância crítica de entender as complexas interações entre condições metabólicas e saúde reprodutiva masculina.

Palavras chaves: síndrome metabólica; próstata; vesícula seminal, fertilidade, estudo translacional

ABSTRACT

CARVALHO, M.G. **PROTEIN SIGNATURES OF THE ANNEX GLANDS AND TESTICLES OF OBESE AND DIABETIC RATS**. Botucatu – SP 2024. 424p. Defesa (Doutorado). Faculdade de Medicina Veterinária e Zootecnia, Campus Botucatu, Universidade Estadual Paulista.

The increasing incidence of obesity and diabetes represents a significant challenge for global public health. In the age group of young individuals in reproductive age, the prevalence of these conditions is alarming, reaching 19.8% for obesity and 8.5% for diabetes. Furthermore, these diseases are linked to hormonal and erectile dysfunction, compromising the morphology and quality of spermatozoa. The inflammatory processes and oxidative stress resulting from irregularities in glucose and insulin signaling are determining factors for the atrophy and functional deterioration of testicles and associated glands, significantly contributing to male infertility. In this regard, there is an intention to understand the effects of metabolic syndrome on testicular, prostatic, and seminal vesicle function, using proteomics to identify biomarkers for the diagnosis or prognosis of male infertility. Thirty Wistar rats approximately 50 days old were used, divided into 3 groups: control (n = 10), diabetic (n = 10), and obese (n = 10). The obese group received a cafeteria diet and ad libitum water with 5% sucrose for 38 weeks, while the control and diabetic groups received balanced commercial feed and ad libitum water simultaneously. The animals were weighed once a week to evaluate weight evolution for Lee index calculation. Diabetes was induced by administering a single dose of 35 mg/kg streptozotocin, and animals with body weight loss and blood glucose levels equal to or greater than 200 mg/dL were considered diabetic. The testicles, prostate, and seminal vesicle were dissected and prepared for proteomics using shotgun approach (CEUA, n 0212/2022). The data underwent multivariate analysis (principal component analysis) and univariate analysis (ANOVA and Fisher LSD test). ROC curves were constructed for treated groups (diabetic or obese) versus control, considering AUC > 0.80 and $P < 0.05$. In the principal component analysis (PCA) performed on the prostate and seminal vesicle fluid, a clear separation was observed only in the diabetic group, highlighting the identification of 23 and 8 proteins, respectively, with differential abundance. In the testicle, PCA revealed a distinction between control, diabetic, and obese groups, as evidenced by the heatmap. In this context, 80 proteins with differential abundance were identified, distributed in different cellular locations such as cytoplasm, sperm cell acrosome, mitochondria, and nucleus. Most of these proteins are produced in human testicles. Additionally, in the analysis of protein-protein interactions, relevant pathways were identified, such as Wnt and spliceosome, along with alterations in enzymatic activities of glycolysis/gluconeogenesis pathways. This study reveals that the identified proteins are closely linked to androgenic activity, sperm motility, cellular integrity, protection against oxidative stress, and fertilization. These findings offer valuable insights into potential biomarkers associated with accessory glands and testicular cells in the context of diabetes and obesity. Notably, the effects were more pronounced among diabetic individuals, while compensatory mechanisms were observed in obese individuals. These conclusions highlight the critical importance of understanding the complex interactions between metabolic conditions and male reproductive health.

Keywords: metabolic syndrome; prostate; seminal vesicle, fertility, translational study

SUMÁRIO

CAPÍTULO 1

1 INTRODUÇÃO E JUSTIFICATIVA

O peso médio da população tem se modificado rapidamente ao longo dos anos e, durante gerações, a curva de distribuição tem crescido de forma exponencial, e o peso humano continua se elevando, afetando homens, muitas vezes jovens e na fase reprodutiva. Em 2019, a obesidade já ocupava o 5º lugar no ranking mundial de doenças que levam ao óbito (Ritchie and Roser, 2020). A evolução global (%), em relação ao aumento da prevalência da obesidade em adultos (> 18 anos), com excesso de peso (IMC > 30), é de 19,8% sendo 16,2% em homens. No Brasil a prevalência é de 22,1% na população e 18,5% em homens. A estimativa é, que até 2035, a prevalência no Brasil seja 41% na população adulta (Lobstein et al., 2023; Wisevoter, 2023a).

Segundo a Sociedade Brasileira de Endocrinologia e Metabologia (SBEM) (Tschiedel, 2014), a obesidade é caracterizada pelo acúmulo excessivo de gordura corporal no indivíduo, causada pela predisposição genética, maus hábitos alimentares ou disfunção endócrina. Em homens, o ideal é que o tecido adiposo corresponda a 20% do peso corporal (Marques and Langouche, 2013). O diagnóstico da obesidade é realizado pelo índice de massa corporal (IMC), parâmetro utilizado pela OMS (WHO, 2018). A obesidade tem etiologia complexa e é associada a diversas comorbidades, elevando o risco de doenças crônicas cardíacas, derrame e diabetes *mellitus* (Pedersen, 2013; Wisevoter, 2023a).

O termo diabetes *mellitus* descreve o distúrbio metabólico com diversas etiologias, alterando o metabolismo de proteínas, gorduras, carboidratos, devido a danos na ação e/ou secreção da insulina (Alberti and Zimmet, 1999; Roglic et al., 2005). Assim como a obesidade, a doença apresenta elevada incidência e abrangência mundial, acometendo também jovens na fase reprodutiva, cuja prevalência é de 9,3% em pessoas com idades acima de 18 anos, de 2000 a 2019 a taxa de mortalidade aumentou 3%, sendo a causa direta de 1,5 milhões de mortes ao ano (WHO, 2023a). No Brasil a prevalência é de 8,8% (Wisevoter, 2023b). Portanto, considerando que essas comorbidades sistêmicas possam coexistir, a avaliação, compreensão e o tratamento voltado para reprodução, de ambas as doenças, assumem uma importância crucial.

Segundo a Organização Mundial da Saúde (WHO, 2023b) estima-se que 17,5% (1 a cada 6 indivíduos) das pessoas adultas ao redor do mundo apresentam infertilidade, sendo a síndrome metabólica, um dos fatores masculinos (Heryanto et al., 2022; Y. Zhang et al., 2023). A fertilidade é definida como a capacidade de gerar descendentes normais, condição essencial para o progresso genético, podendo ser alterada por condições que afetam a capacidade de cópula e/ou habilidade dos espermatozoides fecundarem o oócito (Bicudo et al., 2007). Em humanos, atualmente estima-se que a infertilidade atinja 8% a 15% dos casais em idade reprodutiva (Cui, 2010). São considerados inférteis casais que não usam métodos contraceptivos durante 12 meses, e não conseguem engravidar, (WHO, 2023b) aproximadamente 35% dos casos, a infertilidade é causada por fatores masculinos ou femininos, 20% fatores masculinos e 10% fatores desconhecidos (Matos, 2019). Assim poderíamos dizer, que 55% são fatores masculinos.

As implicações genéticas na ocorrência de obesidade são raras, sendo originada por diversos fatores, como alterações ambientais e comportamentais (Malik, Hu, 2012; Nascimento et al., 2008). Por esse motivo modelos experimentais poligênicos de obesidade induzida por dietas, são preferencialmente utilizados, mimetizando a fisiopatologia da doença, levando a melhor compreensão da síndrome metabólica, e consequente diabetes (Brown, Panchal, 2011; Nilsson et al., 2012).

Em vista da prevalência da obesidade e das comorbidades associadas, como o diabetes, ambas atuando na síndrome metabólica e consequentemente sobre a fertilidade masculina, este estudo teve como objetivo identificar os efeitos da doença sobre a capacidade reprodutiva de ratos obesos e diabéticos. Embora sejam de abrangência mundial ainda permanece inconclusivo, a influência dessas doenças e suas associações no sistema reprodutivo. Desta forma, este estudo visa identificar suas consequências no eixo reprodutivo, utilizando a abordagem proteômica do testículo, próstata e vesícula seminal, em busca de possíveis biomarcadores da infertilidade masculina.

A associação entre as comorbidades e as ações deletérias na função reprodutiva masculina é multifatorial, isso dificulta o entendimento das vias pelas quais ocorrem as principais alterações moleculares, levando a uma diversificada tradução de proteínas no tecido alvo. Ademais, os estudos translacionais utilizam diferentes metodologias e modelos experimentais, para indução da obesidade e diabetes, somado a isso, existem poucos estudos que avaliam ambas as doenças no mesmo delineamento experimental e que usam proteômica do sistema reprodutivo de obesos e diabético.

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